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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/786,317	04/27/2001	Masatoshi Hagiwara	04276.00002	8076

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EXAMINER	
WALICKA, MALGORZATA A	
ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 09/21/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	09/786,317	HAGIWARA ET AL.	
	Examiner	Art Unit	
	Malgorzata A. Walicka	1652	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 09 August 2004 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☐ The period for reply expires _____months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1.☒ A Notice of Appeal was filed on *09 August 2004*. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2.☐ The proposed amendment(s) will not be entered because:

(a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

(b) ☐ they raise the issue of new matter (see Note below);

(c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

(d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: _____.

3.☒ Applicant's reply has overcome the following rejection(s): see the attached.

4.☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5.☒ The a)☒ affidavit, b)☐ exhibit, or c)☐ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *see the attached*.

6.☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7.☒ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: *none*.

Claim(s) objected to: *5*.

Claim(s) rejected: *4, 9,13*.

Claim(s) withdrawn from consideration: _____.

8.☒ The drawing correction filed on *02 March 2001* is a)☒ approved or b)☐ disapproved by the Examiner.

9.☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10.☐ Other: _____

The Amendment and Response to Final Office Action and Declaration under 37 CFR §132, filed August 9, 2004, are acknowledged. Claims 6-8, and 10-12 have been canceled by the current amendment. Claims 9 and 13 have been amended. Claims 4-5, 9 and 13 are currently pending and are the subject of this Advisory.

An appeal under 37 CFR 1.191 was filed in this application on August 9, 2004. Appellant's brief is due in accordance with 37 CFR 1.192(a).

The amendment filed August 9, 2004 under 37 CFR 1.116 in reply to the final rejection has been entered, but is not deemed to place the application in condition for allowance; see bellow. For purposes of appeal, the status of the claims is as follows:

Allowed claim(s): none

Rejected claim(s): 13, 4 and 9

Claim(s) objected to: claim 5

1. Amendments to the specification

The examiner acknowledges the amendments to the specification

2. Rejections

2.1. 35 USC, section 112, second paragraph

Rejection of claim 9 under 35 U.S.C. 112, second paragraph, is withdrawn because the claim has been amended.

2.2. 35 USC, section 112, first paragraph

2.2.1. Lack of written description

Rejection of claims 13, 4 and 9 under 35 U.S.C. 112, first paragraph is maintained for the following reasons.

Claims 13, 4 and 9 are directed to a genus of monitor proteins, and their use, said proteins comprising a) a phosphorylation region that undergoes a conformational change upon phosphorylation and b) a pair of fluorescent proteins, wherein a fluorescent protein of the pair is bound to each opposite end of the phosphorylation region and wherein the conformational change causes a change of the intensity of emitted fluorescence of the monitor protein. The specification is teaches only one phosphorylation region that undergoes a conformational change upon phosphorylation and may be successfully used to construct a monitor protein, i.e., SEQ ID NO: 1 A monitor protein containing SEQ ID NO: 1 is the only true representative species of the claimed genus of the monitor proteins, because of change in fluorescence resonance energy transfer when SEQ ID NO: 1 of ART is phosphorylated Applicants' own data regarding Kempart protein provide evidence that constructing the monitor protein according to claim 13 may not result in the claimed invention. Applicants failed to set forth any identifying characteristic of the other representatives of the genus.

On page 9, line 20 of the specification Applicants write,

"The phosphorylation region is preferably a partial sequence of a protein comprising an amino acid residue to be phosphorylated but can also be the full length protein. For instance, in the case of CREB transcription factor, it is known that the serine residue at amino acid 133 is phosphorylated by proteinase A. Therefore, any partial sequence of CREB transcription factor can be used as

long as it contains the serine residue at amino acid 133 and is capable of being phosphorylated [emphasis added]." However, the sequence of CREB is not disclosed or incorporated by reference in the specification, therefore a polypeptide that contains the serine residue at amino acid 133 lacks written description.

In conclusion, the monitor protein as currently claimed has to be identified by reciting the amino acid structure of the phosphorylation region as not all the members of the genus of proteins comprising part (a) and (b) as claimed in claim 13 are monitor proteins.

2.2.2. Scope of enablement

Claims 13 and 4 and 9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for monitoring protein consisting of for two green fluorescence proteins form *Aequorea victoria* attached to both ends of the phosphorylation region having amino acid sequence of SEQ ID NO: 1, wherein said protein is produced by expression of pETIC-ART plasmid, does not reasonably provide enablement for any pair of fluorescent proteins whose fluorescence is changed by phosphorylation of any phosphorylation region of any sequence of amino acids; see the above rejection for lack of written description. The scope of the claims covers any fusion protein, and method of its use, wherein said fusion protein comprises any phosphorylation region that undergoes a conformational change upon phosphorylation, and any pair of fluorescent proteins wherein said pair of fluorescent protein shows a

change of fluorescence caused by the change of conformation of the phosphorylation caused by its phosphorylation .

The claims are broader in scope than the enablement set forth in the specification. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Otherwise, undue experimentation is necessary to make the claimed invention. Factors to be considered in determining whether undue experimentation is required are summarized *In re* Wands [858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)]. The Wands factors are: (a) the nature of the invention, (b) the breadth of the claim, (c) the state of the prior art, (d) the relative skill of those in the art, (e) the predictability of the art, (f) the presence or absence of working example, (g) the amount of direction or guidance presented, (h) the quantity of experimentation necessary.

The nature and breath of the claimed invention encompasses any fusion protein that shows change of fluorescence of fluorescent proteins caused by phosphorylation of its phosphorylation region. The components of the fusion protein have to be from any organism or man-made. Although production of hybrid protein is well known in the art and skills of artisan high, to make and use the claimed invention is not in the realm of routine experimentation. Applicants provide only the guidance regarding the use of two fluorescent proteins and SEQ ID NO: 1 as components of the fusion monitor protein. Applicants themselves provided evidence that some fusion proteins such as Kempart, do not work as monitor protein; see the above rejection for lack of written description. Thus, it is unpredictable what phosphorylation region should be fused such that there

will be a change in the fluorescence of fusion protein after phosphorylation of the phosphorylation region. The disclosure does not teach how to select phosphorylation region and fluorescent proteins. Thus, one skilled in the art is forced to make a DNA construct encoding a phosphorylated region flanked by fluorescent proteins, express said construct and test the protein for the property of being phosphorylated as well as being able to change the fluorescence in response to phosphorylation. Without further guidance on the part of Applicants as to the nature and structure of the phosphorylation region experimentation left to those in the art is improperly extensive and undue.

4. Examiner's response to Declaration under 37 CFR §132

The Declaration under 37 CFR 1.132 filed August 9, 2004 is insufficient to overcome the rejection of claim 13, 4 and 9 based upon lack of written description and scope of enablement as set forth in the last Office action. Claim 5 is objected as depending on rejected claim 13 and would be allowable if rewritten to include all of the limitations of the base claim.

Regarding claims 13, 4 and 9, although Applicants provide evidence that phosphorylation region which consists of amino acids 4-22 of SEQ ID NO: 1 of the instant application alone, or flanked by specific sequences as shown in the Declaration's Table, can be used for construction of a monitor protein. The phosphorylation sequences listed in the Table are not representative species that identify the whole genus of the monitor protein as claimed and as such cannot be included in the claims because they consist a new matter.

To place the case in conditions for allowance the examiner proposed, on September 9, 2004, that claim 13 included the limitation of claim 5. The examiner's proposal was not accepted by Applicants.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Malgorzata A. Walicka, Ph.D., whose telephone number is (571) 272-0944 and the right fax number is (571) 273-0944. The examiner can normally be reached Monday-Friday from 10:00 a.m. to 4:30 p.m. EST.

If attempts to reach examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, Ph.D. can be reached on (571) 272-0928. The fax phone number for this Group is 703.872.9306.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionists whose telephone number is (703) 308-0196.

Malgorzata A. Walicka, Ph.D.
Art Unit 1652
Patent Examiner

REBECCA E. PROUTY
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